REMARKS

Claims 1, 2, 4, 7, 8, and 21-27 are currently pending in the application. Applicants hereby cancel claim 5. Claims 1, 7, and 21 are in independent form.

Claims 21-24 stand rejected under 35 U.S.C. § 112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. Specifically, the Office Action holds that the phrase "from the delivered mRNA" is unclear and renders the claims indefinite. In response thereto, Applicants have amended the claims to delete the phrase "from the delivered mRNA." Reconsideration of the rejection is respectfully requested.

Claims 21, 23, and 24 stand rejected under 35 U.S.C. § 112, 1st paragraph, as failing to comply with the written description requirement. Specifically, the Office Action holds that the claims encompass a method comprising the delivery of three mRNAs (of claim 21, claim 23, and claim 24) whereas the specification discloses a method of delivering two mRNAs not three mRNAs as required by claim 24. The Office Action holds that since claim 24 depends from claims 23 and 21, claims 23 and 21 must encompass delivering three mRNAs as well. In response thereto, Applicants amended claim 24 to read as a further defined mRNA of claim 21, instead of a separate third mRNA. Claims 21, 23, and 24 now encompass the delivery of two types of mRNA as disclosed in the specification. Reconsideration of the rejection is respectfully requested.

Claims 1, 2, 4, 5, 7, 8, and 21-24 stand rejected under 35 U.S.C. § 112, 1st paragraph because the specification does not reasonably provide enablement for the full scope encompassed by the claims. The Office Action holds that the nature of the invention is the augmentation of wound healing, i.e. all of the claims encompass

augmenting wound healing by delivering mRNA(s) encoding protein(s) that are functionally related to protein synthesis. Specifically, the Office Action states that claim 5 indicates that the method of claim 1 is useful for wound healing, and therefore, claims 1, 2, and 4 must encompass wound healing as well. Further, since the only cells described in the specification as in need of protein synthesis are wound cells, claims 7 and 8 must encompass wound healing. Claims 21-24 explicitly indicate that the method is a method of augmenting wound healing.

The nature of Applicants' invention is not limited to wound healing. Applicants note that claim 5 has been deleted so that wound healing is not read into claims 1, 2, and 4. The present invention is not a method of delivery of a growth factor mRNA to cells, but rather a method of delivery of a eukaryotic translation initiator mRNA, and more specifically, a eukaryotic translation initiation factor 4 (eIF4) mRNA, to harvest higher amounts of proteins without changing the mRNA translation profile due to increased activity of protein synthesis machinery. This technology is used to *either* (a) harvest increased levels of cellular proteins (as in claims 1, 2, 4, 7, and 8), or (b) increase collagen synthesis and tensile strength of wounds by administering mRNA encoding a eukaryotic translation initiator in combination with or without an mRNA encoding a growth factor (as in claims 21-24).

Claims 1, 2, 4, 7, and 8 are not related to wound healing. Wound healing after treatment with eIF4 mRNA will only occur in wound cells. If there is no wound, the wound healing mechanisms to increase protein synthesis would not be triggered. Claims 1, 2, and 4 are related to a method of increasing mRNA translation without changing the protein synthesis profile. These claims relate to the fact that the present invention can be used to increase protein levels of a desired protein when its mRNA is not available. It was demonstrated that when a rat was treated with an eIF4E mRNA, protein synthesis was increased as evidenced by an increased EGF protein

level. This result demonstrated that (a) the eIF4E mRNA was delivered to a cell, (b) the eIF4E protein was produced, (c) the eIF4E proteins were properly phosphorylated by a kinase, (d) the phosphorylated eIF4E protein made a complex with capped mRNA and (e) mediated 43S ribosome binding to mRNA on the AUG codon to initiate translation. (See Figure 1 of Gringras A.-C., et al., Annu. Rev. Biochem. 1999. 68:913-963). Applicants show in Table 4 that increased EGF protein levels after the delivery of the eIF4E mRNA proved that all translational activity (caused by the increased eIF4E levels) was increased. This proved that other cellular protein levels were also increased because the eIF4 mRNA did not discriminate capped mRNAs for initiation of the mRNA translation. Thus, the present invention as defined in claims 1, 2, 4, 7, and 8 is a method to obtain an mRNA translation profile in the cell with proportionally increased cellular proteins after the delivery of eukaryotic translation initiator mRNA. An analogy for this is PCR replication of a DNA sequence; however, only one DNA sequence is replicated by PCR.

Claims 21-24 are related to wound healing, and specifically, they disclose a method to increase collagen synthesis and tensile strength of wounds after eukaryotic translation initiator mRNA treatment with or without co-treatment of EGF mRNA. Support for the amendment of claim 21 can be found on pages 1, 4, 8, 16, 17, 24, 25, 26 and Tables 1-3 in the specification. Epidermal growth factor (EGF) facilitates wound healing. It increases tensile strength of wounds. EGF mRNA delivery increases only the EGF-dependent wound healing pathway activity. This is only one segment of numerous wound healing mechanisms (see Figure 2, Steenfos). Applicants disclosed that eIF4E mRNA treatment increased tensile strength of wounds of chemotherapy-treated (Table 2) and normal (Table 3) animals approximately 25-65%. Considering that there are proteins inhibitory to wound healing, e.g. eIF2 kinase which inhibits translation initiation process, it is surprising that delivery of eIF4 mRNA in the cells produced strong beneficial effects on wound healing.

The Office Action further states in the Nature of the Invention section that the invention is in a class which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Applicants note that Qiu, et al. previously demonstrated predictability of the method of delivering a mRNA by a gene gun to increase its protein level. Specifically, Qiu, et al. increased human alpha-1 antitrypsin protein level in mouse after the delivery of human alpha-1 antitrypsin mRNA. Sohn, et al. (in which the primary authors Murray and Dulchavsky are present inventors) also demonstrated predictability of this method. Applicants show in the present invention that eIF4 mRNA was delivered using the established method. Thus, this invention should not be categorized as an unpredictable art.

As to the Breadth of the Claims section, the Office Action holds that the claims are very broad and encompass a vast number of different mRNAs, including mRNAs that are in any way functionally related to protein synthesis, as well as mRNAs encoding initiation factors wherein the initiation factor can be any factor that is capable of initiating protein synthesis. Applicants note that the claims have been amended significantly to narrow their breadth. Specifically, the subfamily of "mRNA encoding eukaryotic translation initiator" is claimed now instead of the whole group of "mRNA encoding initiation factors". The data in the application is related to eukaryotic translation initiator mRNA, and even more specifically, the eIF4 subfamily of mRNA. Also, the phrase "mRNA functionally related to protein synthesis" has been deleted to narrow the claims. The phrase "a translational regulatory protein functionally related to protein production" has been changed to "an activator of a eukaryotic translation initiator." Applicants have specified "epidermal growth factor" instead of "growth factors" in general. "Wound healing" has also been further defined as "collagen synthesis and tensile strength of wounds." The claims as amended are not overly broad and encompass the invention as described in the specification.

The Office Action holds in the Unpredictability of the Art and the State of the Prior Art section that Qiu, et al. teaches delivering an mRNA encoding human growth hormone (GH) to cells *in vitro* and *in vivo* such that the mRNA expresses the GH protein in the cells. The Office Action holds that Steenfos teaches that growth factors and growth hormone were applied for wound healing and that specific growth factors are recognized as necessary for wound healing, but not all growth factors are necessary for wound healing. Qiu, et al. does not teach delivering mRNA encoding growth hormone to cells *in vivo*, but only *in vitro* (p. 263-4). Applicants are not claiming growth factors in general, but rather are claiming a specific growth factor – epidermal growth factor (EGF). Also, Applicants do not apply EGF mRNA alone to promote collagen synthesis and tensile strength of wounds, but only in combination with eukaryotic translation initiator mRNA.

The Office Action also holds in this section that translation regulatory proteins which increase the synthesis proteins in a cell were also known in the art. Hiremath, et al. synthesized *in vitro* eIF4E mRNA and produced eIF4E mRNA protein using a cell-free reticulocyte translation system, which is well known in the art. After the eIF4E proteins were produced, Hiremath, et al. found that the eIF4E protein was bound to the cap structure of mRNA and was a part of a 48S initiation complex which contained 40S ribosome. This finding is known in the art and drastically differs from the finding of the Applicants. Hiremath, et al. produced the eIF4E protein in a cell-free system which did not involve any difficulty of cell membrane crossing of the mRNA, whereas the mRNA in the present invention crossed the cell membrane. Hiremath, et al. proved that the eIF4E protein was co-eluted with the 48S region in the sucrose gradient chromatography fractions but did not prove whether addition of eIF4E mRNA increased other protein levels in the cell. Applicants show in Table 4 that not just eIF4E mRNA level increases, but also EGF mRNA level increases. In other words, all

the protein in the cell increases, because the protein translation machinery does not discriminate which protein will increase. If one mRNA increases, all the mRNA levels will increase. Hiremath, et al. further failed to discuss use of the method (e.g. increasing cellular protein levels without changing translated protein profile or increasing collagen synthesis and tensile strength of wounds) other than elucidating eIF4E binding molecules.

In the Working Examples and Guidance in the Specification section, the Office Action holds that the specification discloses working examples wherein specific mRNA encoding specific proteins (i.e. EGF and eIF4E) are delivered to wound cells for augmenting wound healing. Applicants point out that the disclosure in the specification is not limited to wound healing. Claims 1, 2, 4, 7, and 8 are not related to wound healing and rather relate to increasing a protein synthesis level without changing the protein translation profile after eukaryotic translation initiator mRNA delivery. Also, Applicants do not claim "administering a mRNA encoding a growth factor (specifically EGF) in combination with a mRNA encoding the translation initiation factor eIF4E to the cells" as the Office Action states, but rather "administering a mRNA encoding a eukaryotic translation initiator in combination with a mRNA encoding growth factor (specifically EGF) to the cells." In other words, Applicants do not claim a treatment of EGF mRNA alone.

In the Quantity of Experimentation section, the Office Action holds that considering the limited amount of working examples and guidance provided by the specification, in view of the breadth of the claims, additional experimentation would be required. As discussed above, Applicants have amended the claims extensively to narrow their scope. Thus, the specification discloses sufficient working examples and guidance to practice the amended claims to their full scope.

In the Level of Skill in the Art section, the Office Action holds that the level of skill in the art is high. Extensive literature on gene therapy with DNA delivery to a cell, a tissue, or an organ has been published. Recently, mRNA delivery (see Qiu, et al.) to cell, tissue, and organ has been successfully developed using exactly the same method used for DNA delivery (see Cheng, et al., Yang, et al., and reference therein). The delivery method disclosed in the present application is very similar to the known method. The main difference between the DNA and mRNA deliveries is that, whereas proteins expressed after RNA delivery is transient, proteins expressed after DNA delivery is permanent. Thus, the level of skill in the art is not high.

Therefore, considering the narrow breadth of the amended claims, the teachings of the prior art, the working examples and guidance in the specification that match the amended claims, and the level of skill in the art not being high, Applicants have shown that the amount of experimentation required to perform the claimed invention is not undue. Reconsideration of this rejection is respectfully requested.

Claims 1, 2, and 4 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Qiu, et al. (Gene Therapy, 1996). Specifically, the Office Action holds that Qiu, et al. teaches a method comprising delivering an mRNA encoding human Growth Hormone (GH) to cells *in vitro* and *in vivo* wherein the mRNA is delivered by gene gun delivery. The Office Action holds that growth factors, including growth hormone, are well recognized in the art as factors which activate cellular proliferation and gene expression in cells. Given the broadest reasonable interpretation of the claims in view of the definitions provided by the specification, an mRNA encoding Growth Hormone is an mRNA encoding an initiation factor functionally related to protein synthesis and therefore, Qiu, et al. anticipates the instant claims. Reconsideration of the rejection under 35 U.S.C. § 102(b), as anticipated by Qiu, et al., as applied to the claims is respectfully requested. Anticipation has always been held to

require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

In Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986) it was stated: "For prior art to anticipate under §102 it has to meet every element of the claimed invention."

In Richardson v. Suzuki Motor Co., Ltd., 868 F.2d 1226, 9 U.S.P.Q.2d 1913 (Fed. Cir. 1989) it was stated: "Every element of the claimed invention must be literally present, arranged as in the claim."

As stated above, Qiu, et al. does not teach delivering mRNA encoding growth hormone to cells *in vivo*, but only *in vitro*. Qiu, et al. discloses no data concerning protein increase after delivering growth hormone *in vivo*. Applicants note that claim 1 as currently amended is drawn to the delivery of mRNA encoding a eukaryotic translation initiator alone. Applicants do not disclose the delivery of mRNA encoding a growth hormone alone. Growth hormones and translation initiation factors are neither the same in structure nor in function. Growth hormones are not capable of binding to capped mRNA and transforming the mRNA to be in the 48S state to initiate mRNA translation, unlike translation initiation factors. Since the Qiu, et al. reference does not disclose the delivery of a eukaryotic translation initiator as set forth in the presently pending independent claim, the claim is patentable over the Qiu, et al. reference and reconsideration of the rejection is respectfully requested.

Claims 1, 5, 7, 8, 21, 22, and 23 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Qiu, et al. (Gene Therapy, 1996) in view of Steenfos (Scand. Journal Plastic Reconst. Hand Surgery, 1994; Vol. 28, pages 95-105). Specifically, the Office Action holds that the claims are very broad and encompass a

vast number of mRNAs. The Office Action holds that Qiu, et al. teaches the general concept that mRNA encoding a gene of interest can be delivered to a cell using gene gun particle acceleration such that the mRNA is delivered into the target cell and the gene of interest encoded by the delivered mRNA is expressed in the cell, and therefore, it would have been obvious to use the method of Qiu, et al. to deliver and express ANY gene of interest in a cell. The Office Action holds that an mRNA encoding growth hormone is an mRNA encoding an initiation factor functionally related to protein synthesis. Further, the Office Action holds that Steenfos teaches that human GH is a growth factor that is useful in treating wounds. Therefore, it would have been *prima facie* obvious to combine the teachings of Qiu, et al. and Steenfos to create a method of treating wounds (which includes cells that are in need of increased protein synthesis) by delivering mRNA encoding human GH cells of a wound in order to augment wound healing with a reasonable expectation of success. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over the Qiu, et al. and Steenfos references is respectfully requested.

It is Hornbook Law that before two or more references may be combined to negate patentability of a claimed invention, at least one of the references must teach or suggest the benefits to be obtained by the combination. This statement of law was first set forth in the landmark case of Ex parte McCullom, 204 O.G. 1346; 1914 C.D. 70. This decision was rendered by Assistant Commissioner Newton upon appeal from the Examiner-in-Chief and dealt with the matter of combination of references. Since then many courts have over the years affirmed this doctrine.

The applicable law was more recently restated by the Court of Appeals for the Federal Circuit in the case of ACS Hospital Systems, Inc. v. Montefiore

Hospital, 732 F.2d 1572,1577, 221 U.S.P.Q. 929 (Fed. Cir. 1984). In this case the Court stated, on page 933, as follows:

> "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under Section 103 teachings of references can be combined only if there is some suggestion or incentive to do so. The prior art of record fails to provide any such suggestion or incentive. Accordingly we hold that the court below erred as a matter of law in concluding that the claimed invention would have been obvious to one of ordinary skill in the art under section 103."

This Doctrine was even more recently reaffirmed by the CAFC in Ashland Oil, Inc. v. Delta Resins and Refractories, Inc., et al., 776 F.2d 281,297, 227 U.S.P.Q. 657,667. As stated, the District Court concluded:

> "Obviousness, however, cannot be established by combining the teachings of the prior art to produce the claimed invention unless there was some teaching, suggestion, or incentive in this prior art, which would have made such a combination appropriate."

The Court cited ACS Hospital Systems, Inc. in support of its ruling. This Doctrine was reaffirmed in In re Deuel, 34 USPQ2d 1210 (Fed. Cir. 1995).

Qiu, et al. teaches mRNA delivery of human growth hormone to a cell (*in vitro* only) to successfully produce the growth hormone protein. The function of the human growth hormone was not studied (thus, correct folding or post-translational modification of the protein is not known). Qiu, et al. also teaches human alpha-1 antitrypsin (hAAT) mRNA delivery to cells (*in vitro*) and to a mouse (*in vivo*). Qiu, et al. found that the hAAT proteins were expressed in the cell but the function of the protein was not studied. The mechanism of Qiu, et al. can be summarized as follows: hAAT mRNA treatment via gene gun transfection → crossing cell membrane → translated to hAAT protein by the constitutive translation

machinery in the cell → hAAT protein secreted into blood → antibody production. During the *in vivo* study, Qiu, et al. found that the hAAT mRNA delivery induced an immune reaction which produced antibodies of the hAAT (p. 265 and Fig. 2). This production of an immune response was the purpose of the hAAT treatment. Most likely, the human AAT and mouse AAT amino acid sequences were poorly conserved so that the human AAT was foreign to the mouse.

As discussed above, the claims of the presently pending invention have been narrowed significantly and as such the presently pending invention is neither disclosed nor suggested by the Qiu, et al. reference. The present invention and claims are directed to delivering eukaryotic translation initiator mRNA to a cell to (a) produce eukaryotic translation initiator protein from the mRNA by the constitutive translation machinery in the cell followed by correct phosphorylation of the correctly folded protein, and (b) initiate translation after the eukaryotic translation initiator protein binds to capped mRNA and causes the mRNA to adopt the right position in 48S containing 40S ribosome. The 40S binds to 60S and this 60S initiation factor translates the mRNA in the cell. Thus, eukaryotic translation initiator mRNA treatment increases general cellular protein levels without changing the mRNA translation profile. Further, the claims of the presently pending invention are directed to the delivery of eukaryotic translation initiator mRNA with or without co-delivery of EGF mRNA to increase collagen synthesis and increase tensile strength of wounds.

The mRNA species to be delivered and the procedure, mechanism and purpose of delivery as disclosed by Applicants drastically differ from Qiu, et al., who found and invented antibody production technology by hAAT mRNA delivery. The mechanism of the present invention can be summarized as follows using eIF4 mRNA: eIF4 mRNA treatment via gene gun transfection → crossing cell membrane → translated to eIF4 protein by the constitutive translation machinery in the cell →

correct folding of eIF4 protein → phosphorylation of the eIF4 protein → binding to capped mRNA → producing 48S initiation complex bound on AUG of the capped mRNA → producing 60S initiation complex → translating mRNAs including EGF mRNA → increasing general cellular protein levels. Applicants are the first to show this unexpected process. Also, in contrast to the AAT, the eIF4 subfamily is a well conserved protein. From the teachings of Qiu, et al., it would be expected that delivery of a foreign mRNA *in vivo* would produce an immune response. However, eIF4 does not induce an undesired immunological response.

The statement "an mRNA encoding Growth Hormone is an mRNA encoding an initiation factor functionally related to protein synthesis" is simply not true. The mRNA encoding human GH of Qiu, et al. is much different than the mRNA of the present invention. Growth hormone cannot carry out translation initiation of an mRNA in a cell because it cannot recruit a capped mRNA to a 43S ribosome to produce the 48S complex. Growth hormone has its own GenBank number different from translation initiation factors. Eukaryotic translation initiators have GenBank numbers distinct from growth hormone. Therefore, growth hormone and translation initiators are functionally and genetically unrelated molecules.

The Office Action states that "Steenfos teaches that human growth hormone is a growth factor that is useful for treating wounds; Steenfos teaches that growth hormone has an anabolic action in stimulation of protein synthesis; From the wound healing aspect, increased protein synthesis may be important both in improving healing and decreasing healing time; Systematic treatment with growth hormone in rats increased mechanical strength." Growth hormone is NOT a growth factor but induces a growth factor (IGF-1), which is involved in healing. Growth hormone, also called somatotropin, is a 191 amino acid peptide and "not a local growth factor" (Steenfos, p. 100). Growth hormone may increase protein synthesis.

Growth hormone induces IGF-1 levels which facilitates wound healing. However, high levels of growth hormone induced dermal hypertrophy in wound moderately in female and severely in male mice (Wanke, et al., 1999, J. Investig. Dermatol. 113, 967-971). This is a unique symptom induced by the growth hormone in wounds. In contradistinction, Applicants disclosed that eIF4 increased protein synthesis in the wound. The eIF4 protein is not a secreted protein. Growth hormone is a secreted protein circulating in blood. Its powerful influence cannot be limited to the local wound healing. Growth hormone is produced by a pituitary gland in the brain. Wound cells do not express growth hormone mRNA. Thus, treatment of eukaryotic translation initiator mRNA cannot increase growth hormone levels in the wound cells or in circulation.

Steenfos teaches that growth factors and growth hormone have been applied to human wounds in clinical trials to study the effects of wound healing. This is known in the art and discussed in Applicants' specification on pages 2-4. Steenfos is silent as to any translation initiation factors that may be applied for wound healing, and further, there is no indication in Steenfos that translation initiation factors would be useful in wound healing. Applicants' invention is not directed to a treatment of growth factor or growth hormone mRNA, but to the treatment of eukaryotic translation initiator mRNA to increase protein synthesis (for wound healing in claims 21-24). In order for a eukaryotic translation initiator to function correctly, it must be correctly folded to exert its activity. Applicants are the first to show that eIF4 was expressed and correctly folded and was able to increase protein synthesis and augment wound healing. Applicants are also the first to carry out a co-treatment of a growth factor (EGF) mRNA and a eukaryotic translation initiator mRNA for synergistic wound healing (claim 22). EGF does not induce growth hormone. Steenfos does not teach or suggest the beneficial wound healing effect of co-treatment of eukaryotic

translation initiator mRNA and EGF mRNA. Combining the invention of Steenfos with that of Qiu, et al. would not arrive at the present invention.

Since neither the cited references alone or in combination with knowledge in the art suggest the currently claimed invention, it is consequently respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above. The prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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